Published by Elsevier Inc.

ISSN 0735-1097/03/$30.00
doi:10.1016/S0735-1097(03)00645-4

Plasma C-Reactive Protein as a Marker of Cardiac Allograft Vasculopathy in Heart Transplant Recipients

Aina Hognestad, MD,* Knut Endresen, MD, PHD,* Ragnhild Wergeland, MS,† Oddvar Stokke, MD, PHD,† Odd Geiran, MD, PHD,‡ Torbjorn Holm, MD, PHD,* Svein Simonsen, MD, PHD,* John K. Kjekshus, MD, PHD,* Arne K. Andreassen, MD, PHD*

Oslo, Norway

OBJECTIVES This study was initiated to determine whether heart transplant recipients (HTRs) with cardiac allograft vasculopathy (CAV) have increased levels of high-sensitivity C-reactive protein (hsCRP) and to examine whether an increase in hsCRP after heart transplantation predicts the development of CAV. Furthermore, the effect of pravastatin on plasma levels of hsCRP in HTRs was investigated.

BACKGROUND The relationship between CAV and hsCRP, as well as the effect of statins on hsCRP in HTRs, has not been well established.

METHODS On referral for their annual angiographic control study, 150 consecutive HTRs (mean 6.5 years since transplantation) were included. Plasma levels of hsCRP were measured before angiography and compared with patients with (n = 52) and without (n = 98) CAV. In 49 of these patients, we additionally analyzed hsCRP in blood samples stored from their six-month visit after the transplantation procedure. Furthermore, in a randomized, crossover study, hsCRP was analyzed in 17 male HTRs before and after six weeks of treatment with 20 mg pravastatin.

RESULTS Median levels of CRP were elevated among patients with CAV compared with those with normal angiograms [3.86 (1.78 to 7.00) vs. 1.08 (0.72 to 2.13) mg/l, $p < 0.001$]. Prospectively evaluated hsCRP levels from six months to follow-up were significantly higher among those who developed CAV compared with those with normal angiograms [+2.76 (1.56 to 5.00) vs. +0.07 (−0.57 to 0.41) mg/l, $p < 0.001$]. On multivariate analysis, the increase in hsCRP was the only significant predictor of CAV. Six weeks of treatment with pravastatin significantly reduced hsCRP levels by 25%, without any relation to changes in lipid values.

CONCLUSIONS Elevated plasma levels of CRP are associated with angiographic evidence of CAV, and the increase in hsCRP is a strong predictor of development of CAV. Statin treatment reduces levels of hsCRP and should be used in HTRs, regardless of their lipid levels. (J Am Coll Cardiol 2003;42:477–82) © 2003 by the American College of Cardiology Foundation

Cardiac allograft vasculopathy (CAV), an accelerated and diffuse form of coronary atherosclerosis, determines long-term function of the transplanted heart and is the major cause of death after the first year of heart transplantation (1).

See page 483

The disease is thought to be multifactorial in origin and has been suggested to result most likely from initial and ongoing immunologically mediated injury to the vascular endothelium (2). The most common diagnostic tool of CAV detection is routine annual coronary angiography, recommended because cardiac ischemia can develop without symptoms until severe cardiac dysfunction and death occur (3,4). It is assumed that early detection of CAV may result in the implementation of early surgical, percutaneous, or medical life-saving therapies.

High-sensitivity C-reactive protein (hsCRP) is an acute-phase protein and is a sensitive indicator of acute and chronic inflammation occurring in the body. A growing number of studies suggest that hsCRP is an independent risk factor for native atherosclerotic disease (5). In a recent morphologic report, hsCRP levels correlated with the severity and extension of coronary artery disease (6). It has also been suggested that elevated hsCRP levels predict allograft failure (7). This raises the possibility of applying the marker to identify high-risk patients for CAV, thus reducing the regular screening angiography in otherwise stable heart transplant recipients (HTRs).

The purpose of this study was to compare plasma levels of hsCRP with angiographic evidence of CAV in a large cohort of HTRs and to determine whether patients with CAV have increased levels of hsCRP. We also wanted to examine whether the increase in hsCRP after heart transplantation can predict the development of CAV. Furthermore, it is well established that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) protect against CAV. Because this effect is not clearly attributable to lipid lowering (8,9), we tested the effect of pravastatin on inflammatory activity determined by plasma hsCRP levels,

From the Departments of *Cardiology, †Clinical Chemistry, and ‡Thoracic Surgery, Rikshospitalet, Oslo, Norway.

Manuscript received November 15, 2002; revised manuscript received March 17, 2003, accepted March 27, 2003.

Abbreviations and Acronyms

BMI = body mass index
CAV = cardiac allograft vasculopathy
HLA = human leukocyte antigen
hsCRP = high-sensitivity C-reactive protein
HTR = heart transplant recipient
ROC = receiver-operating characteristics

evident in most but not all reports on statin treatment in native atherosclerosis (10,11).

METHODS

A total of 150 consecutive patients without signs of infection or acute rejection, who underwent routine annual follow-up after heart transplantation, were entered into the study between April 2001 and February 2002. The mean time since transplantation was 6.5 years (range 1 to 16 years). All patients gave written, informed consent. The indication for heart transplantation was end-stage heart failure due to ischemic heart disease (n = 64), idiopathic cardiomyopathy (n = 60), or miscellaneous disorders (congenital, valvular disease, myocarditis; n = 26). Standard triple-immunosuppressive therapy consisted of cyclosporine, corticosteroids, and azathioprine. A statin has been used routinely in our unit for all patients postoperatively since 1997.

Venous blood samples were obtained from the patients after an overnight fast before angiography was performed. Blood samples were collected from an antecubital vein into pyrogen-free tubes containing heparin (Becton Dickenson, San Jose, California) and centrifuged at 1,400*g* for 10 min at room temperature. The hsCRP was measured by an immunonephelometric assay performed on the Behring nephelometer (BN II, Dade Behring, Deerfield, Illinois). The patients underwent routine annual coronary angiography. Operators performing the procedure were blinded to hsCRP measurements. The diagnosis of CAV was classified as mild, moderate, or severe on the basis of involvement of the left main coronary artery, primary-vessel stenosis, and branch-vessel stenosis (12,13). Patients were categorized into two groups: those with angiographically normal and those with abnormal coronary arteries.

In a subgroup of 49 patients, blood samples stored at −80°C from their six-month visit after transplantation were also analyzed for hsCRP. The increase in hsCRP from six months to follow-up, with a mean follow-up of 4.8 ± 1.7 years, was compared between those who developed CAV (n = 14) and those who did not (n = 35).

In addition to the aforementioned investigations, we analyzed hsCRP in 17 male HTRs (mean [±SEM] age 53 ± 3 years) in an open-label, crossover design study, randomized to receive either 20 mg pravastatin or no treatment for six weeks. After a six-week washout period, patients were crossed over. None of the patients participating in this substudy had previously received statin treatment. The mean time since transplantation in this group was 6 years (range 1 to 15 years). Measurements were performed at baseline, after six weeks of treatment, and after discontinuation of treatment.

Table 1. Patient Characteristics

	CAV+ (n = 52)	CAV− (n = 98)
Age (yrs)	58 ± 10	50 ± 15*
Years since therapy	8.7 ± 4.0	6.5 ± 3.7*
Etiology (CAD/non-CAD)	34/18	42/56*
Gender (M/F)	43/9	75/23
BMI (kg/m^2)	28.1 ± 3.8	25.8 ± 4.5*
Smokers	15/37 (29%)	10/88 (10%)*
Total cholesterol (mmol/l)	5.8 ± 1.6	5.4 ± 1.1
HDL cholesterol (mmol/l)	1.3 ± 0.4	1.6 ± 0.5*
Cyclosporine (μg/l)	120.0 ± 45.9	114.2 ± 34.4
Creatinine (μmol/l)	145.1 ± 54.0	116.9 ± 24.9*
Statin use	47/5 (90%)	85/13 (87%)
ASA use	20/32 (38%)	7/91 (7%)
Time of ischemia (min)	141.5 ± 62.9	136.4 ± 68.8
Donor age (yrs)	30.4 ± 11.2	31 ± 11.9
Gender mismatch	9/43 (17%)	28/70 (29%)
CMV mismatch	30/22 (58%)	46/52 (47%)

Data are presented as the mean value ± SD or n/N (%) of patients.
ASA = acetyl salicyclic acid (aspirin); BMI = body mass index; CAD = coronary artery disease; CAV = cardiac allograft vasculopathy; CMV = cytomegalovirus; HDL = high-density lipoprotein.

Statistical analysis. Continuous data are presented as the mean value (±SD) for variables with normal distribution, as the median value (interquartile range) for variables with a skewed distribution, or as the frequency for categorical variables. The skewness test was performed to evaluate whether the data were normally distributed. The Student *t* test was used to compare geometric mean values, whereas the Mann-Whitney *U* test was used to compare median values. Categorical variables were compared by chi-square analysis. Logistic regression analysis was applied to identify predictors of CAV, and the variables used were those which gave significant differences between the two groups on univariate analysis. A receiver-operating characteristics (ROC) curve was generated to evaluate the accuracy of hsCRP in the prediction of CAV (measured by the area under the ROC curve, range 0.5 to 1). The median level of hsCRP was selected as a cutoff point. A Kruskal-Wallis test was performed to evaluate the association between hsCRP levels and severity of CAV. In the crossover study, the change in hsCRP was calculated as the median change during treatment and after discontinuation, as compared with baseline values. A p value <0.05 was considered statistically significant.

RESULTS

Patient characteristics. Among the 150 patients included in the study, 52 had angiographic evidence of CAV. A history of ischemic heart disease and smoking was significantly more frequent in the group with CAV (Table 1). Furthermore, these patients were significantly older than

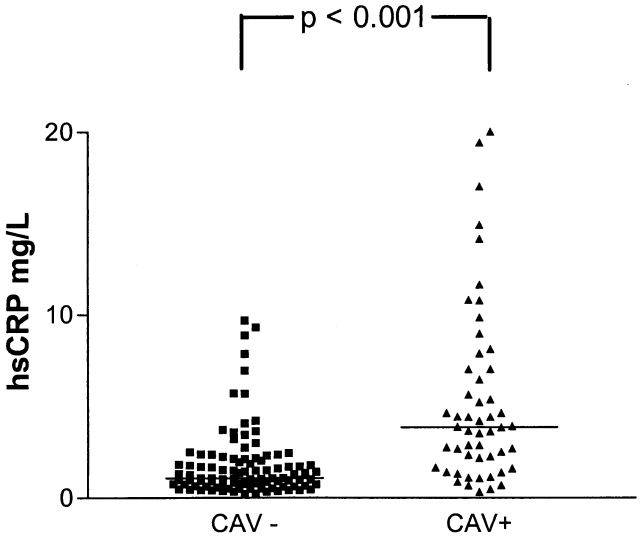

Figure 1. Levels of high-sensitivity C-reactive protein (hsCRP) among patients with normal angiograms **(squares)** and patients with angiographic evidence of cardiac allograft vasculopathy (CAV) **(triangles)**. The **horizontal line** indicates the median of the hsCRP values.

those with normal angiograms and had a significantly longer time since transplantation, increased body mass index (BMI), glycosylated hemoglobin, creatinine, and lower high-density lipoprotein cholesterol levels (Table 1). There was no difference in the numbers or severity of cellular rejections between the two groups, nor was there any difference regarding cytomegalovirus status, time of ischemia during the transplantation procedure, human leukocyte antigen (HLA) mismatch, or donor age.

hsCRP and CAV. The median level of hsCRP for the whole cohort was 1.66 mg/l (0.84 to 3.66). As assessed with a similar technique in our laboratory, a median level of 0.90 mg/l was recently found in 105 healthy individuals (14). Patients with evidence of CAV had significantly elevated hsCRP levels compared with those with normal angiograms [3.86 (1.78 to 7.00) and 1.08 (0.72 to 2.13) mg/l, $p < 0.001$] (Fig. 1). When classifying all patients into groups according to increasing levels of CRP, a significant association with the frequency of CAV was observed across quartiles: 4 (11%), 8 (21%), 13 (34%), and 27 (75%) patients with CAV, respectively ($p < 0.001$ for trend), giving an odds ratio between the fourth and first quartiles of 24.75 (95% confidence interval [CI] 6.86 to 89.31) (Fig. 2). The ROC analysis indicated that hsCRP had reasonable accuracy for the development of CAV (Fig. 3). A cutoff point of hsCRP at 1.66 mg/l gave a sensitivity of 77% and a specificity of 64% for the development of CAV. There was a significant trend toward higher hsCRP values in advanced stages of CAV (Fig. 4).

Predictors of CAV and levels of hsCRP. On multivariate analysis, using CAV as the dependent variable, hsCRP together with patient age and time since transplantation were significant predictors of CAV, whereas BMI was borderline significant (Table 2). A significant interaction between BMI and hsCRP was evident ($p = 0.001$ for interaction). Smoking was not an independent predictor of CAV, but a significant interaction between smoking and hsCRP was observed ($p = 0.02$ for interaction).

Prospective study. Baseline hsCRP levels at six months after transplantation did not differ between patients who developed CAV and those with normal angiograms [1.37 (0.91 to 2.11) vs. 1.04 (0.61 to 1.97) mg/l, p = NS], nor did the time to follow-up (5.3 ± 1.7 years vs. 4.8 ± 1.8 years, p = NS). In the former group, hsCRP levels increased significantly from baseline to follow-up, compared with patients without CAV [2.76 (1.56 to 5.00) mg/l vs. 0.07 (−0.57 to 0.41) mg/l, $p < 0.001$] (Fig. 5). On multivariate analysis, the increase in hsCRP from baseline to follow-up was the only significant predictor of CAV in this subgroup.

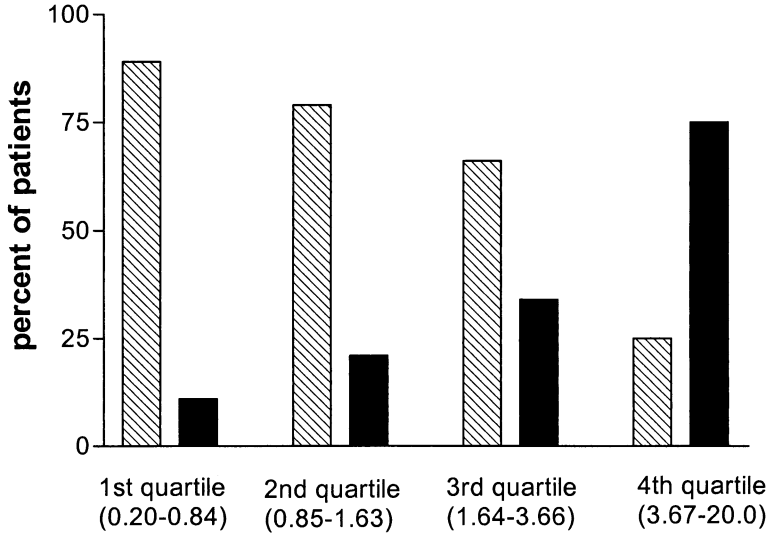

Figure 2. Numbers of patients with normal angiograms **(lined bars)** and with angiographic evidence of cardiac allograft vasculopathy **(solid bars)** in each quartile of high-sensitivity C-reactive protein levels. The odds ratio between the first and fourth quartile is 24.75 (95% confidence interval 6.86 to 89.31).

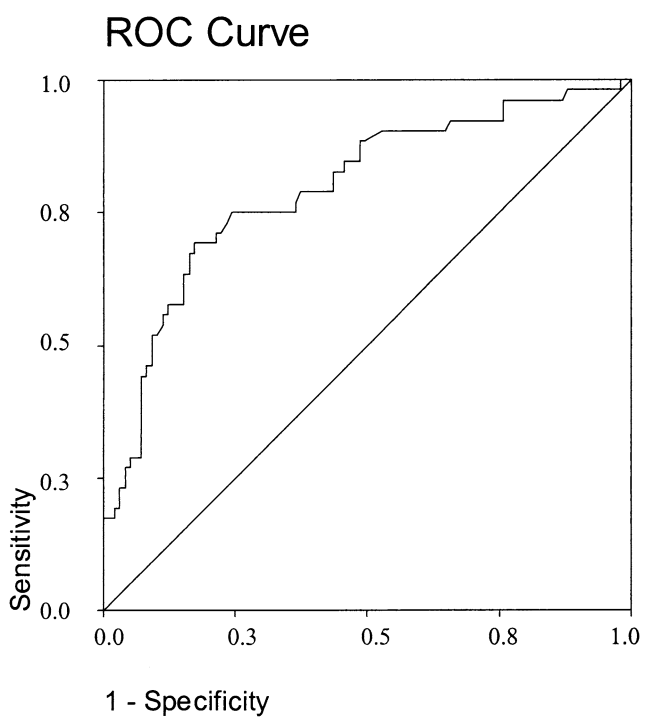

Figure 3. The receiver operating characteristics (ROC) curve of high-sensitivity C-reactive protein as a marker for cardiac allograft vasculopathy. The ROC area was 0.80 (95% confidence interval 0.72 to 0.87; $p < 0.001$).

Crossover study. Six weeks of treatment with 20 mg pravastatin significantly reduced hsCRP relative to baseline values [from 2.21 (0.77 to 3.28) to 1.64 (0.81 to 2.35) mg/l, $p = 0.01$]. After another six weeks of washout, hsCRP increased to baseline values [2.15 mg/l (0.79 to 6.65), p = NS vs. baseline and $p < 0.01$ vs. after 6 weeks of treatment]. Although pravastatin induced significant reductions in levels of both total and low-density lipoprotein cholesterol ($p < 0.01$ for both), no correlation was found between changes in lipids and hsCRP levels (data not shown).

Table 2. Multivariate Predictors of Cardiac Allograft Vasculopathy

Risk Factors for CAV	OR	95% CI	p Value
Age	1.07	1.01–1.13	0.029
Years since transplantation	1.23	1.07–1.42	0.004
Etiology	0.63	0.23–1.63	0.327
BMI	1.14	0.99–1.32	0.064
Smoking	2.75	0.77–10.82	0.147
HDL cholesterol	0.44	0.11–1.72	0.241
Creatinine	1.01	0.99–1.03	0.292
hsCRP	1.31	1.06–1.61	0.012

CI = confidence interval; hsCRP = high-sensitivity C-reactive protein; OR = odds ratio; other abbreviations as in Table 1.

DISCUSSION

This study demonstrates that HTRs with CAV can be identified by higher plasma levels of hsCRP, compared with those without angiographic evidence of disease. Furthermore, a long-term rise in hsCRP represents an independent predictor of CAV development. The observed pravastatin-mediated reductions in hsCRP levels extend the observation of anti-inflammatory properties of statins in HTRs, supporting their widespread prophylactic use in the prevention of CAV.

hsCRP and CAV. Cardiac allograft vasculopathy results from a complicated interplay between immunologic and nonimmunologic factors, with consequent repetitive vascular injury and a localized sustained inflammatory response (2). This vascular remodeling process involves the local migration and proliferation of medial vascular smooth muscle cells in response to inflammatory signals such as cytokines and growth factor expression, with consequent thickening of the intima (15). Elevated levels of hsCRP in patients with CAV probably reflect these processes. The pathogenesis of the inflammatory reactions leading to elevated hsCRP is not known. Unlike another recent study (7), we were unable to find any major differences between

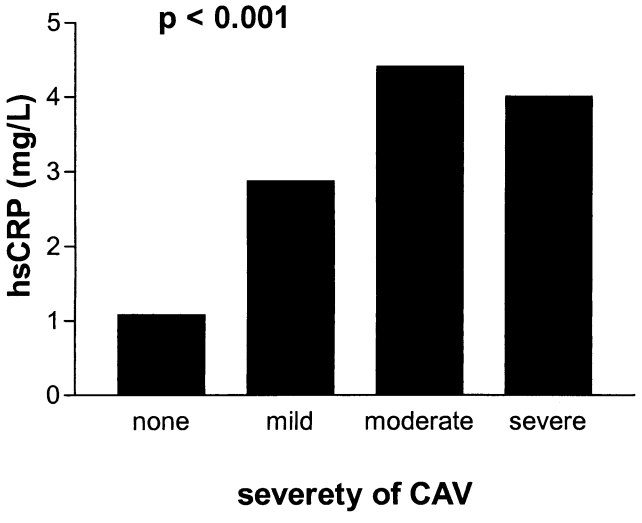

Figure 4. Median levels of high-sensitivity C-reactive protein (hsCRP) by severity of cardiac allograft vasculopathy (CAV).

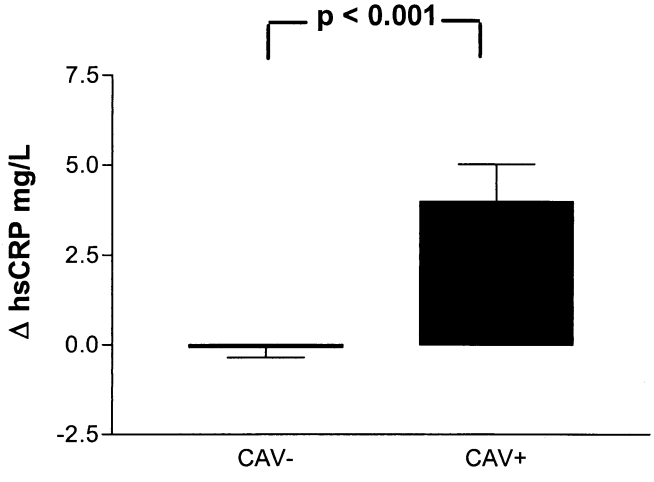

Figure 5. Delta values (expressed as mean values) of high-sensitivity C-reactive protein (hsCRP) from baseline to follow-up among patients with normal angiograms (cardiac allograft vasculopathy [CAV]−) and in patients with angiographic evidence of CAV (CAV+).

patients with and without CAV regarding immunologic factors such as HLA mismatch and the number of cellular rejections, or nonimmunologic risk factors such as donor characteristics, time of ischemia, and cytomegalovirus infection. Interestingly, traditional risk factors in the development and progression of atherosclerosis were present in the group with CAV. Although smoking was not an independent predictor of CAV in our study, a significant interaction between smoking and hsCRP was observed. It has previously been shown that smoking is associated with an increase in CRP (16) and with intima-media thickness in carotid arteries (17). Thus, despite a lack of a direct relationship between smoking and CAV in our study, smoking could increase hsCRP, either by nurturing inflammation or by other not yet identified mechanisms. The mechanism by which BMI predisposes to CAV is not clear. Adipose tissue produces interleukin-6, which has proinflammatory properties by stimulating acute-phase proteins in the liver (18). This may explain the observed interaction between hsCRP and BMI. Further, it is well known that high-density lipoprotein cholesterol has a protective role in native atherosclerosis. Even though conventional atherosclerotic risk factors do not necessarily predict the development of CAV, it has been shown that metabolic abnormalities are associated with more severe vasculopathy (19,20), findings that are supported by this study. In fact, CAV development was recently shown to develop in a rat model where there were no major or minor histocompatibility mismatches (21), highlighting the importance of nonimmune factors. In concordance with other studies (13,22,23), we also found that older age and pretransplant ischemic heart disease was more frequent among patients with CAV.

We do not know if the inflammation reflected by hsCRP is the cause of CAV or whether it is just a manifestation of the disease. Instead of being just a marker for systemic inflammation, CRP may also have a pathogenetic role. It has been shown that CRP can activate complement and stimulate production of tissue factor by mononuclear cells (24). In addition, elevated levels of hsCRP are associated with impaired systemic endothelial vascular reactivity in patients with native atherosclerosis (25), and endothelial dysfunction is believed to contribute to progression of coronary artery disease and to future cardiovascular events (26,27). Reduced endothelium-dependent vasodilation is well documented also in HTRs (28), and the observed relationship between hsCRP and CAV in this study may partly be explained by this phenomenon. This is further supported by Labarrere et al. (29), who showed that elevated hsCRP was associated with increased levels of intercellular adhesion molecule-1. It was previously shown that CRP induces expression of intercellular adhesion molecule-1 in coronary artery endothelial cells (30). Without challenging the view of an early perioperative insult to the endothelium as the initial trigger, our prospective investigation of hsCRP underlines the importance of individual chronic inflammatory responses leading to CAV. We found that hsCRP is markedly elevated in patients with emerging CAV, and it seems to be a quantitative marker of the progression of the disease. These findings are in concordance with two other recent studies (29,31) and give additional support to the association between CAV and systemic inflammation. Whether elevated hsCRP is a risk marker or a risk factor will only be settled by future studies.

In search of improved noninvasive indicators and techniques that can more clearly define the groups of patients at higher risk for CAV (4), our study findings could have clinical implications in terms of reducing the number of angiographic procedures. Because high levels of hsCRP seem to represent a marker of CAV development in individual patients, transplant centers should include this measurement in their routine blood samples. Due to the degree of overlap between values in patients with and without CAV, hsCRP determination is not suitable as a single noninvasive parameter in deciding the need for invasive procedures. However, a role of hsCRP levels as an ancillary method for exclusion of CAV seems justified, so that there is a less rigid use of angiography in these patients.

Statins and hsCRP. Our demonstration of a median 25% reduction of hsCRP after only six weeks of treatment with a relatively low dose of pravastatin in HTRs, is at least as affective as the results achieved in native atherosclerosis and hyperlipidemia (32,33). Furthermore, the observation adds this patient group to those with various forms of cardiovascular disease, where this phenomenon has been documented. Although it seems a common trait among different statins, not all patients with latent or manifest cardiovascular disease respond to statins with lowering of hsCRP (10,11). In familial hypercholesterolemia, levels of hsCRP were reported to be higher in those with than in those without atherosclerotic disease, but statin treatment over one year had no significant effect on hsCRP levels (10). It could be speculated that the inflammatory aspect is more essential among HTRs than in familial hypercholesterolemia. The recent demonstration of reductions in levels of proinflammatory cytokines and improvement of coronary endothelial function with statin treatment after heart transplantation suggests their important roles in improving graft survival and reducing CAV in long-term postoperative treatment with statins (34). Alterations in endogenous factors such as cytokines seem a plausible mechanism by which statins reduce hsCRP levels also in HTRs, rather than by increasing the clearance or reducing the synthesis of hsCRP.

Study limitations. Characterization of CAV was performed by semi-quantitative angiographic grading. It is known from intravascular ultrasound studies that these results can be misleading in terms of a possible underestimation of intimal hyperplasia and vascular remodeling (31,35). Thus, it cannot be determined whether the relationship between hsCRP and CAV would have been strengthened or weakened by the latter technique.

Conclusions. Elevated plasma levels of hsCRP are associated with angiographic evidence of CAV, and the increase in hsCRP during follow-up of HTRs is a strong predictor of the development of CAV. These findings demonstrate the importance of inflammation in this disease, and hsCRP could be used as an ancillary marker for detection of CAV during follow-up of HTRs. Statin treatment reduces levels of hsCRP in these patients, giving further evidence of their ability to lower inflammatory activity, leading to fewer cases of CAV. Our results concur with the recent report of Labarrere et al. (29) and can be extended to have clinical implications in that pravastatin decreases hsCRP in HTRs.

Reprint requests and correspondence: Dr. Aina Hognestad, Department of Cardiology, Rikshospitalet, Sognsvannsveien 20, N-0027 Oslo, Norway. E-mail: aina.hognestad@klinmed.uio.no.

REFERENCES

1. Cooke GE, Eaton GM, Whitby G, et al. Plasma atherogenic markers in congestive heart failure and post-transplant (heart) patients. J Am Coll Cardiol 2000;36:509–16.
2. Weis M, von Scheidt W. Cardiac allograft vasculopathy: a review. Circulation 1997;96:2069–77.
3. Aranda J, Pauly D, Kerensky R, et al. Percutaneous coronary intervention versus medical therapy for coronary allograft vasculopathy: one center's experience. J Heart Lung Transplant 2002;21:860–6.
4. Sechtem U. Do heart transplant recipients need annual coronary angiography? Eur Heart J 2001;22:895–7.
5. Blake GJ, Ridker PM. High sensitivity C-reactive protein for predicting cardiovascular disease: an inflammatory hypothesis. Eur Heart J 2001;22:349–52.
6. Burke AP, Tracy RP, Kolodgie F, et al. Elevated C-reactive protein values and atherosclerosis in sudden coronary death: association with different pathologies. Circulation 2002;105:2019–23.
7. Eisenberg MS, Chen HJ, Warshofsky MK, et al. Elevated levels of plasma C-reactive protein are associated with decreased graft survival in cardiac transplant recipients. Circulation 2000;102:2100–4.
8. Wenke K, Meiser B, Thiery J, et al. Simvastatin reduces graft vessel disease and mortality after heart transplantation: a four-year randomized trial. Circulation 1997;96:1398–402.
9. Kobashigawa JA, Katznelson S, Laks H, et al. Effect of pravastatin on outcomes after cardiac transplantation. N Engl J Med 1995;333:621–7.
10. Mohrschladt MF, de Maat MP, Westendorp RG, Smelt AH. C-reactive protein in patients with familial hypercholesterolemia: no effect of simvastatin therapy. Atherosclerosis 2001;157:491–4.
11. Joukhadar C, Klein N, Prinz M, et al. Similar effects of atorvastatin, simvastatin and pravastatin on thrombogenic and inflammatory parameters in patients with hypercholesterolemia. Thromb Haemost 2001;85:47–51.
12. Gao SZ, Alderman EL, Schroeder JS, Silverman JF, Hunt SA. Accelerated coronary vascular disease in the heart transplant patient: coronary arteriographic findings. J Am Coll Cardiol 1988;12:334–40.
13. Costanzo MR, Naftel DC, Pritzker MR, et al. Heart transplant coronary artery disease detected by coronary angiography: a multiinstitutional study of preoperative donor and recipient risk factors. Cardiac Transplant Research Database. J Heart Lung Transplant 1998;17:744–53.
14. Wergeland R, Oyen O, Bentdal O, Stokke O. MicroCRP: a highly sensitive CRP method applied in the monitoring of renal allograft recipients. Scand J Clin Lab Invest 1999;59:405–16.
15. Radovancevic B, Poindexter S, Birovljev S, et al. Risk factors for development of accelerated coronary artery disease in cardiac transplant recipients (with discussion). Eur J Cardiothorac Surg 1990;4:309–13.
16. Zevin S, Saunders S, Gourlay SG, Jacob P, Benowitz NL. Cardiovascular effects of carbon monoxide and cigarette smoking. J Am Coll Cardiol 2001;38:1633–8.
17. Wallenfeldt K, Hulthe J, Bokemark L, Wikstrand J, Fagerberg B. Carotid and femoral atherosclerosis, cardiovascular risk factors and C-reactive protein in relation to smokeless tobacco use or smoking in 58-year-old men. J Intern Med 2001;250:492–501.
18. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. JAMA 1999;282:2131–5.
19. Valantine H, Rickenbacker P, Kemna M, et al. Metabolic abnormalities characteristic of dysmetabolic syndrome predict the development of transplant coronary artery disease: a prospective study. Circulation 2001;103:2144–52.
20. Kapadia SR, Nissen SE, Ziada KM, et al. Impact of lipid abnormalities in development and progression of transplant coronary disease: a serial intravascular ultrasound study. J Am Coll Cardiol 2001;38:206–13.
21. Cantin B, Wen P, Zhu D, et al. Transplant coronary artery disease: a novel model independent of cellular alloimmune response. Circulation 2001;104:2615–9.
22. Aziz T, Burgess M, Rahman AN, Campbell CS, Yonan N. Cardiac transplantation for cardiomyopathy and ischemic heart disease: differences in outcome up to 10 years. J Heart Lung Transplant 2001;20:525–33.
23. John R, Rajasinghe HA, Itescu S, et al. Factors affecting long-term survival (>10 years) after cardiac transplantation in the cyclosporine era. J Am Coll Cardiol 2001;37:189–94.
24. Danesh J, Whincup P, Walker M, et al. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. BMJ 2000;321:199–204.
25. Fichtlscherer S, Rosenberger G, Walter DH, Breuer S, Dimmeler S, Zeiher AM. Elevated C-reactive protein levels and impaired endothelial vasoreactivity in patients with coronary artery disease. Circulation 2000;102:1000–6.
26. Meredith IT, Anderson TJ, Uehata A, Yeung AC, Selwyn AP, Ganz P. Role of endothelium in ischemic coronary syndromes (with discussion). Am J Cardiol 1993;72:27–32C.
27. Zeiher AM. Endothelial vasodilator dysfunction: pathogenetic link to myocardial ischaemia or epiphenomenon? Lancet 1996;348 Suppl 1:S10–2.
28. Davis SF, Yeung AC, Meredith IT, et al. Early endothelial dysfunction predicts the development of transplant coronary artery disease at 1 year post-transplant. Circulation 1996;93:457–62.
29. Labarrere CA, Lee JB, Nelson DR, Al-Hassani M, Miller SJ, Pitts DE. C-reactive protein, arterial endothelial activation, and development of transplant coronary artery disease: a prospective study. Lancet 2002;360:1462–7.
30. Pasceri V, Willerson JT, Yeh ET. Direct proinflammatory effect of C-reactive protein on human endothelial cells. Circulation 2000;102:2165–8.
31. Pethig K, Heublein B, Kutschka I, Haverich A. Systemic inflammatory response in cardiac allograft vasculopathy: high-sensitive C-reactive protein is associated with progressive luminal obstruction. Circulation 2000;102 Suppl III:III233–6.
32. Jialal I, Stein D, Balis D, Grundy SM, Adams-Huet B, Devaraj S. Effect of hydroxymethyl glutaryl coenzyme A reductase inhibitor therapy on high sensitive C-reactive protein levels. Circulation 2001;103:1933–5.
33. Azar RR, Waters DD. PRINCE's prospects: statins, inflammation, and coronary risk. Am Heart J 2001;141:881–3.
34. Weis M, Pehlivanli S, Meiser BM, von Scheidt W. Simvastatin treatment is associated with improvement in coronary endothelial function and decreased cytokine activation in patients after heart transplantation. J Am Coll Cardiol 2001;38:814–8.
35. Julius BK, Attenhofer Jost CH, Sutsch G, et al. Incidence, progression and functional significance of cardiac allograft vasculopathy after heart transplantation. Transplantation 2000;69:847–53.